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Award Number: DAMD17-01-1-0236

TITLE: Evaluation of Feasibility for a Case-Control Study of
Pituitary-Ovarian Function in Premenopausal Women with
Breast Cancer

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REPORT DATE: July 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY
(Leave blank)**2. REPORT DATE**
July 2004**3. REPORT TYPE AND DATES COVERED**
Annual (1 Jul 03-30 Jun 04)**4. TITLE AND SUBTITLE**

Evaluation of Feasibility for a Case-Control Study of Pituitary-Ovarian Function in Premenopausal Women with Breast Cancer

5. FUNDING NUMBERS

DAMD17-01-1-0236

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9. SPONSORING / MONITORING**AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSORING / MONITORING
AGENCY REPORT NUMBER****11. SUPPLEMENTARY NOTES**

20041028 139

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE**13. ABSTRACT (Maximum 200 Words)**

Background: Postmenopausal women with elevated estrogens are at an increased risk of breast cancer, but an association of estrogens with breast cancer in premenopausal women has not been clearly established. Objective/Hypothesis: We will evaluate the feasibility of a case-control study that uses gonadotropin releasing hormone (GnRH) agonist stimulation tests to compare pituitary-ovarian function in premenopausal women with breast cancer with unaffected controls. Hypotheses to be tested in the full-scale study are: 1) premenopausal women with breast cancer secretes more luteinizing hormone (LH) and follicle stimulating hormone (FSH) in response to GnRH compared to controls; 2) premenopausal women with breast cancer secrete more estradiol and testosterone in response to gonadotropins, and this is related to their higher insulin like growth factor -1 (IGF-1) levels compared to controls; 3) increased estradiol production in premenopausal women with breast cancer is due to increased enzyme activity at a specific step in steroidogenesis. Specific Aims: Specific aims of the feasibility study are: 1) determine the feasibility of a full-scale study; 2) gather preliminary data on basal and GnRH stimulated serum levels of LH, FSH, estradiol, and testosterone in women with breast cancer compared to controls. Study Design: A case-control study will be conducted at FCCC.

14. SUBJECT TERMS

GnRH

15. NUMBER OF PAGES

6

16. PRICE CODE**17. SECURITY CLASSIFICATION
OF REPORT**

Unclassified

**18. SECURITY CLASSIFICATION
OF THIS PAGE**

Unclassified

**19. SECURITY CLASSIFICATION
OF ABSTRACT**

Unclassified

20. LIMITATION OF ABSTRACT

Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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Introduction: Elevated serum estrogen levels in postmenopausal women have been shown to increase the risk of breast cancer. However, the association of serum estrogens with breast cancer in premenopausal women has not been established. The purpose of this study is to determine the safety and feasibility of conducting a case-control study that uses gonadotropin releasing hormone (GnHR) stimulation tests to evaluate the sensitivity of the hypothalamic pituitary ovarian (H-P-O) axis in premenopausal women with breast cancer compared to unaffected premenopausal women. The full-scale study will determine if: 1) the anterior pituitary of pre-menopausal women with breast cancer secretes more luteinizing hormone (LH) and follicle stimulating hormone (FSH) in response to GnRH compared to controls; 2) the ovaries of pre-menopausal women with breast cancer secrete more estradiol and testosterone in response to gonadotropins, and this is related to their higher insulin like growth factor -1 (IGF-1) levels compared to controls; 3) increased estradiol production by the ovaries in premenopausal women with breast cancer is due to increased enzyme activity at a specific step in steroidogenesis.

Body: Research accomplishments are described for each task outlined in the approved statement of work.

Task 1: Prepare for data collection, Months 1-2

- a. *Finalize data collection protocol and forms.* This activity has been completed and all questionnaires have been approved by both the FCCC IRB and the DOD IRB.
- b. *Finalize database design and data entry screen.* This activity has been completed.
- c. *Hire and train program coordinator.* This activity has been completed.

Task 2. Identify and recruit participants, Months 2-6

- a. *Search the FCCC Tumor Registry and Health Information Management System (HIMS) to identify potential cases and benign breast disease controls.* The FCCC IRB required that we conduct the study in phases – recruiting and conducting GnRH stimulation tests in healthy premenopausal women during the first phase and conducting GnRH stimulation tests in premenopausal women treated for stage 0 or stage 1 breast cancer who did not receive any chemotherapy and who completed adjuvant therapy at least one year earlier during the second phase. Twenty one women who may be potentially eligible for Phase 2 have been identified by using HIMS.
- b. *Obtain physician approval to contact cases and benign breast disease controls.* Physicians have approved a letter drafted to contact their patients who may be eligible for Phase 2. They have not been contacted regarding specific cases because we are awaiting DOD approval of the letter. FCCC IRB had approved this letter in January 2004.
- c. *Identify one friend control who is eligible and agrees to participate for each case.* Friend controls have been replaced with healthy community controls because of the IRB's concerns about asking cases to identify friends who did not have breast cancer. This was approved in the original protocol submitted to the DOD.
- d. *Send approximately 50 letters.* Letters have been sent to 53 women.

- e. *Perform approximately 50 telephone interviews.* As of May 12, 2004, 97 interested, premenopausal women have called in to obtain more information about the study. Twenty-two women were not eligible for participation based on the preliminary screening questionnaire approved by the FCCC and DOD IRBs. Twenty-five women were no longer interested once they received more information about the study. Thirty-nine women were potentially eligible based on the screening interview completed over the phone. An additional 41 women were interested after recruitment for healthy women ceased.

Task 3. Conduct data collection visits, Months 3-8. We have received FCCC IRB and DOD IRB approval of changes to the protocol submitted in June 2003 before beginning data collection visits.

- a. *Administer 27 questionnaires.* Ten questionnaires have been administered.
- b. *Measure heights and weights of 27 participants.* Heights and weights have been measured for 10 participants.
- c. *Perform 27 GnRH stimulation tests, collect and store serum specimens.* Ten GnRH stimulation tests have been performed. These serum specimens were collected and are currently stored in the FCCC Biosample Repository.
- d. *Isolate DNA from lymphocytes for 27 participants and store.* DNA has been isolated for 10 participants and are currently stored in the FCCC Biosample Repository.
- e. *Key and verify data.* Data has been keyed and verified for 10 participants.

Task 4. Create a serum pool for laboratory quality control, Month 8. This task will be done when we get closer to conducting laboratory analyses.

Task 5. Measure LH, FSH, estradiol, testosterone, IGF-1, and IGFBP-3 concentrations in serum from 27 participants, Months 9-10. This task will be done after the GnRH stimulation study. Estradiol has been measured in 10 samples. All results were found to be within normal range. Based on these results the FCC Data and Safety Monitoring Board and the DOD IRB approved continuing to Phase 2 of the study, which involves testing women with a history of stage 0 or 1 breast cancer.

Task 6. Analyze data and write reports, Months 11-12. This task will be completed in the future.

- a. Perform statistical analyses
- b. Write final report
- c. Begin writing grant proposal for full scale study

Key Research Accomplishments:

- Our goal for the first phase of the study is to recruit 10 women.
- Ten women have completed Phase I of the study.
- After Phase I was completed, the study received the approval to continue with Phase II from the FCCC Data Safety Monitoring Board and the DOD IRB.
- Twenty-one women have been identified for Phase II of the study.

Reportable Outcomes: None at this time.

Conclusions: This is an interim report for a pilot study. Based on our experience to date, it appears that we will be able to recruit healthy controls for a full scale case-control study that uses gonadotropin releasing hormone (GnRH) stimulation to determine sensitivity of the hypothalamic pituitary ovarian (H-P-O) axis in premenopausal women with breast cancer compared to unaffected premenopausal women. The full-scale study will also evaluate whether differences in serum IGF-1 and IGFBP-3 contribute to observed differences in ovarian steroidogenesis in premenopausal women with breast cancer and controls. Furthermore, it will determine if increased production of estrogens in premenopausal women with breast cancer following GnRH stimulation is related to increased enzyme activity at a specific step in the steroidogenesis pathway. Identification of the hormonal cause for breast cancer in premenopausal women could ultimately lead to detection of populations at increased risk, approaches to screening for women at high risk, and/or chemopreventive strategies that target the responsible enzyme or regulatory protein.

References: None at this time.

Appendices: None at this time.